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## PATENT ABSTRACTS OF JAPAN

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(54) PERSISTENT CATAPLASM FOR REDUCING PAIN

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a persistent cataplasm for reducing pain excellent in medicinal efficacy, safety and adhesive characteristics by selecting a specific copolymer as an adhesive component, and dissolving lidocaines to a substrate obtained by adding a specified oil component acting as a release-regulator to the adhesive component.

SOLUTION: This cataplasm is obtained by formulating lidocaines as an active ingredient and an oil component selected from a liquid paraffin, a higher fatty acid and a vegetable oil as a release-regulator in a cataplasm substrate including styrene-isoprene styrene block copolymer as an adhesive main component and a tackifier component, and allowing the formulated materials to be carried on a soft supporter. The formulating amounts are 1-30wt.% lidocaines, 5-50wt.% copolymer, 5-60wt.% oil component and 1-60wt.% tackifier. The cataplasm is used for reducing pain of zoster herpes or neuralgia after the zoster herpes, excellent in persistence of the effect and safe because the medicinal efficacy is rapidly diminished after removing the cataplasm.

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CLAIMS

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[Claim(s)]

[Claim 1] The pasting agent for durability pain relief characterized by having blended with the \*\*\*\* basis containing a styrene-isoprene-styrene block copolymer and an adhesion grant component the oil component chosen out of the group which consists of the liquid paraffin, the higher fatty acid, and vegetable oil as the lidocaine and exudation modifier as an active principle, and making it support this on a flexible base material.

[Claim 2] The pasting agent for durability pain relief given in the 1st term of a claim the content of 5 - 50 % of the weight and an oil component is [ the content of a lidocaine / the given content of 5 - 60 % of the weight and an adhesion grant component ] 1 - 60 % of the weight for the content of a 1 - 30 % of the weight, and styrene-isoprene-styrene block copolymer.

[Claim 3] The claim 1st term or chosen out of the group which an adhesion grant component becomes from rosin, a polyterpene resin, an alicycle group saturated-hydrocarbon resin, and rosin ester, the pasting agent for durability pain relief of the 2nd-term publication.

[Claim 4] The pasting agent for durability pain relief of either the claim 1st term or which is what is excellent in the durability of an effect for mitigating the ache of the after [ shingles or shingles ] neuralgai, and is excellent in \*\*\*\* disappearing quickly after elimination at safety, and the 3rd term given in a term.

[Claim 5] The pasting agent for durability pain relief whose \*\*\*\* is what is used for mitigation of the ache of the after [ shingles or shingles ] neuralgai including 1 - 30 % of the weight of lidocaines, 5 - 50 % of the weight of styrene-isoprene-styrene block copolymers, 5 - 60 % of the weight of liquid paraffins, and 1 - 60 % of the weight of alicycle group saturated-hydrocarbon resins.

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DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] this invention relates to a lidocaine and the pasting agent for durability pain relief to which the oil component for raising this absorption can be contained, it can use for because of mitigation of the ache of durability, such as the after [ shingles or shingles ] neuralgai, and percutaneous absorption can be carried out over a long time stably [ component / \*\*\*\* / this ] as a \*\*\*\* component still in detail about the pasting agent for durability pain relief.

[0002]

[Description of the Prior Art] Although a shingles ache and the durability neuralgai after shingles are morbus whose symptoms are shown, they have a nervus block treatment first as main cures to this morbus. [ to an old man ] [ comparatively many ] Although this performs a block of the sympathetic ganglia, a stellate ganglion, and a \*\*\*\* ganglion using local anesthetics, such as a lidocaine, with the case maintained for one year or more, it is almost ineffective and there is a fault that the number of times of the treatment increases. Moreover, although a block dura mater outside is a treatment which uses together a local anesthetic, or it and a steroid, and performs the extradural anesthesia, it has the fault that there is a patient's pain. Furthermore, the present condition is that the effect does not accept enough about a block under an arachnoid membrane, an intravenous-drip method, and a cure called part seepage injection.

[0003] In addition, although there is also a treatment of acupuncture or a cryotherapy, each thing which a cure at large [ these ] can be told is the thing which must be \*\*\*\*ed or sent to hospital for every time of the treatment, and that there is a fault of requiring time and time at the time of the treatment, in order to require the special treatment technique.

[0004] Although it was very useful to have enabled the treatment in a house also from the field of QOL for the patient, the establishment of the effective cure by medicine called the oral agents or medicines for external application other than injection which cannot be performed especially for patient itself, or intravenous drip was desired as one method of realizing it in recent years when it has talked about the aging society. Among these, it is known that there are a manifestation of side effects, such as digestive trouble, and a problem receive a solution in part there since it goes via a liver before reaching a target site (the first time transit effect), and there is a fault of being unable to perform elimination of the medicine after medication further as many oral agents are reported.

[0005] Since it is such, a medicine can be prescribed for the patient for patient itself, and, moreover, endermic medication is attracting attention as high medication gestalt of safety. For example, it is indicated about the local application of the lidocaine constituent by the gel vehicle to processing of the after [ herpes ] neuralgai by JP,2-300138,A. However, although an indication with this official report is the endermic application by the gel splenium treatment and the plaster, since all lack in tackiness, it is necessary to support it with the splenium etc., and it has the fault that it is inferior for practicality.

[0006] On the other hand, the shingles neuralgai and the external application pasting agent for the after [ shingles ] neuralgai treatment are indicated by JP,4-305523,A. This external application pasting agent is a tablet which uses the water-soluble-polymer matter, water, and

a water retention agent as an indispensable component and which made the poultice basis of the so-called drainage system contain a lidocaine or its salt. Although it is carrying out if moisture has the operation which raises the permeability of a medicine in this official report, in fact, it seldom melts in water, but since a crystal may separate in a water-soluble basis when a lidocaine is added in large quantities, a lidocaine has a question in the pharmacology effect. Moreover, although replacing with a lidocaine and using the salt is also considered, it is hard to say that it is matter which is hard to be absorbed and has immediate effect nature from the skin although the lidocaine salt itself tends to melt into water. Therefore, it is estimated as what is hard to be referred to as satisfied [ with this official report ] of the tablet of an indication about absorption of an actual medicine.

[0007]

[Problem(s) to be Solved by the Invention] Thus, it was hard to say that the pasting agent with the practicality suitable for easing durability pain, such as the after [ the present shingles or shingles ] neuralgai, is offered, and was asked for the development of the pasting agent which was more excellent in \*\*\*\*, safety, and the pasting property.

[0008]

[Means for Solving the Problem] Then, this invention persons studied the external application pasting agent which can mitigate the durability pain and which makes a lidocaine an active principle. By the way, a pasting agent is mostly divided roughly into two types of the plaster agent of the poultice of a drainage-system basis, and an oil system (non-drainage system) basis. Since and and water with adhesion comparatively low [ the poultice ] as a result of a preliminary study of this invention persons were included, it knew that there was a field, like it is inferior to the exudation nature and the percutaneous absorption, or the medicine stability of a lidocaine. Moreover, it also knew that many problems were included compared with the basis of an oil system in that change (drug release nature and adhesion are also influenced) of the character by vaporization of the moisture after an application happens. Therefore, it was judged that the tablet of the oil system which does not contain moisture was desirable. However, in order to acquire neither continuous percutaneous absorption nor sufficient tackiness but to obtain the practical lidocaine inclusion pasting agent to the durability pain, the device was still required only by blending a lidocaine with the plaster agent of an oil system basis.

[0009] Then, the result to which both this invention persons repeated the \*\*\*\*\* study for the tablet possessing the continuous percutaneous absorption and the continuous tackiness of a lidocaine in the lidocaine inclusion pasting agent of an oil system, Choose a styrene-isoprene-styrene block copolymer as an adhesion component, and it finds out that the purpose is attained by melting a lidocaine or its salt in the basis which added the specific oil component which acts on this as an exudation modifier, and came to complete this invention.

[0010] That is, this invention blends the oil component chosen out of the group which consists of a liquid paraffin, a higher fatty acid, and vegetable oil as the lidocaine and exudation modifier as an active principle, and provides the \*\*\*\* basis containing the styrene-isoprene-styrene block copolymer and the adhesion grant component with the pasting agent for durability pain relief characterized by making this support on a flexible base material.

[0011]

[Embodiments of the Invention] The pasting agent for durability pain relief of this invention (henceforth a "pasting agent") blends the oil component chosen out of the group which consists of a lidocaine, a liquid paraffin, a higher fatty acid, and vegetable oil into the \*\*\*\* basis containing the styrene-isoprene-styrene block copolymer (it may be hereafter called "SIS") which is an adhesion principal component, and an adhesion grant component, prepares \*\*\*\*, and is manufactured by making this support on a flexible base material by the conventional method.

[0012] the loadings of the lidocaine which is the active principle of this invention -- the fat of a pasting agent -- the inside of the body and 1 - 30 % of the weight (only henceforth "%") are desirable, and 5 - 20% is especially desirable

[0013] SIS which is a basis component is the component which cannot be lacked in order to exhibit tackiness required as a pasting agent. Although \*\*\*\* is obtained even if it uses other matter as an adhesion principal component, SIS is the most desirable when the physical properties of a pasting agent etc. are taken into consideration.

[0014] 5 - 50% of the weight of \*\*\*\* of the loadings of this SIS basis is desirable, and they are more desirable. [ 10 - 40% of ] If fewer than 5%, cohesive force may decline, problems, such as carrying out the paste remainder at the time of pasting, may arise, when 50% is exceeded, it becomes hard too much and an adhesive agent may be produced.

[0015] The oil component chosen out of a liquid paraffin, a higher fatty acid, and vegetable oil softens the binder of \*\*\*\*, and gives exudation of the lidocaine covering a long time, and the flexible physical properties of a pasting agent by blending this while it adjusts the exudation from \*\*\*\* of a lidocaine. therefore, elastic \*\*\*\* of adhering to stability to shingles and morbus, such as the after [ shingles ] neuralgai, for a long time [ effective ], and emitting a lidocaine without [ this ] an oil component in the meantime -- a flexible pasting agent cannot be obtained Especially as this oil component, a liquid paraffin is desirable.

[0016] 5 - 60% of the weight of \*\*\*\* of the loadings of an oil component is desirable, and they are more desirable. [ 10 - 40% of ] If fewer than 5%, the flattery nature to the exudation capacity and the skin covering a long time of a lidocaine will fall, when 60% is exceeded, it may become soft too much, and cohesive force may be lost, and the paste remainder may arise at the time of pasting.

[0017] An adhesion grant component is a resin which begins by combining with a binder and produces tackiness. Unless this adhesion grant component is contained, adhesion does not occur and the function as a pasting agent cannot be achieved. As an adhesion grant component, rosin, a polyterpene resin, an alicycle group saturated-hydrocarbon resin, rosin ester, etc. are desirable, for example. An alicycle group saturated-hydrocarbon resin is desirable also especially of these.

[0018] 1 - 60% of the loadings of this adhesion grant component are desirable, and are especially desirable. [ 20 - 50% of ] When adhesive power will be lost and they will become easy to separate, if there are few amounts of an adhesion grant component than 1%, and they exceed 60%, adhesive power is too strong, an ache may arise at the time of sublation, sublation of a horny layer may happen, and it may become the cause of a skin stimulus.

[0019] In addition, to the external application pasting agent of this invention, softeners, such as perfume, such as anti-oxidants, such as bulking agents, such as titanium oxide used for the general pasting agent other than the above-mentioned indispensable component if needed, and a dibutyl hydroxy toluene, and the peppermint oil, a polybutene, and a polyisobutylene, can be added.

[0020] As mentioned above, the pasting agent of this invention carries out the mixed lysis of the above-mentioned indispensable component, considers as \*\*\*\*, and is prepared by making this support on a flexible base material. If the example is shown, melting mixture is carried out under heating of SIS basis, an oil component, an adhesion grant component, and an arbitrary component, and a lidocaine is added there, and it mixes and is made to melt enough first. Subsequently, after spreading and cooling this \*\*\*\* radiationally to a flexible base material, sublation material is stuck if needed and it can prepare by judging in a suitable area.

[0021] In order to give the flattery nature to a motion of the skin when sticking a pasting agent to a movable site, as for the base material used here, it is desirable to use the material of the shape of the flexible shape of a film and a sheet. As a suitable material, for example, a nonwoven fabric, a vinyl chloride film, the nit, textile fabrics, a polyurethane film, etc. can be illustrated, and a nonwoven fabric and the nit are desirable also especially of this. Especially the thickness of \*\*\*\* formed on a base material has desirable about 100-300 micrometers 50-500 micrometers.

[0022] That from which the content of a styrene-isoprene-styrene block copolymer formed [ the content of a lidocaine ] in the nonwoven fabric (base material) \*\*\*\* whose content of 10 - 30% and an alicycle group saturated-hydrocarbon resin (adhesion grant component) the content of a liquid paraffin (oil component) is 20 - 45% by the thickness of 200-300

micrometers 20 to 40% five to 20% as a desirable mode of the pasting agent of a  
\*\*\*\*\* this invention is mentioned.

[0023] The external application pasting agent of this invention explained above has not only the morbus of the after [ shingles or shingles ] neuralgai but the ache in the case of the laser treatment, a silverfish, and the effect that was excellent also to durability pain, such as an ache in the case of - biopsy, and an ache at the time of the skin graft of a burn, and the treatment of \*\*\*\*\*, at the time of the treatment of \*\*\*\*\*.

[0024]

[Function] It may aim at relief of the case where it aims at relief of the pain at the time of the venipuncture etc., shingles, the ache of the after [ shingles ] neuralgai, etc., etc. in endermic use of a local-anesthetic lidocaine. However, the concept of pain relief of both has a big difference. Namely, what is necessary is in the case of the former, to ask a tablet for immediate effect nature first, and to be able to demonstrate the effect of pain relief only at the time of treatment, such as the venipuncture. On the other hand, it is asked for the durability of an effect how an ache can be rather stopped from immediate effect nature for a long time, in the case of the latter. For that purpose, not only about an effect but about adhesion, although it is good, in the case of the latter, it is asked for the durability of a long time (12 - 24 hours) in about at most 1 hour, and the former must continue fixing to the affected part for a long time. Since the pasting agent of this invention is not only excellent in the durability of a pain relaxation effect, but has the property of excelling also in the tackiness to an application site, and flattery nature, it can be said to the purpose of pain relief of the after [ shingles or shingles ] neuralgai as a very suitable tablet.

[0025]

[Example] Although an example, the example of a comparison, and the example of an examination are given and this invention is explained still in detail hereafter, this invention is not limited to these. In addition, among an example or the example of a comparison, especially the "section" means the "weight section", unless it refuses.

[0026] Example 1 Lidocaine The ten sections Styrene-isoprene-styrene block copolymer 1  
The 22 sections Alicycle group saturated-hydrocarbon resin 2 The 38 sections Liquid paraffin  
The 30 sections Anti-oxidant The 0.1 sections 1 Clayton D-1107 (product made from shell  
\*\*\*\*\*)

2) \*\*\*\*\* P-100 (the Arakawa chemistry company make)

[0027] Melting of each component below a styrene-isoprene-styrene block copolymer was carried out to the bottom of heating, and the lidocaine was added and it mixed. Subsequently, this mixture was spread and cooled radiationally on the nonwoven fabric. A polyethylene-terephthalate film is stuck on this, and it judges in a suitable size, and is a lidocaine 2.14mg/cm  
2 The pasting agent to contain was obtained.

[0028] Example 2 Lidocaine The ten sections Styrene-isoprene-styrene block copolymer 1  
The 25 sections Alicycle group saturated-hydrocarbon resin 2 The 50 sections Liquid paraffin  
The 15 sections Anti-oxidant The 0.1 sections 1 Clayton D-1112 (product made from shell  
\*\*\*\*\*)

2) \*\*\*\*\* P-90 (the Arakawa chemistry company make)

[0029] It is a lidocaine 2.14mg/cm like an example 1 2 The pasting agent to contain was obtained.

[0030] Example 3 Lidocaine The five sections Styrene-isoprene-styrene block copolymer 1  
The 31 sections Alicycle group saturated-hydrocarbon resin 2 The 40 sections Liquid paraffin  
The 14 sections Myristic-acid isopropyl The ten sections Anti-oxidant The 0.1 sections 1  
Queen tackiness 3450 (Nippon Zeon Co., Ltd. make)

2) \*\*\*\*\* P-90 (the Arakawa chemistry company make)

[0031] It is a lidocaine 1.07mg/cm like an example 1 2 The pasting agent to contain was obtained.

[0032] Example 4 Lidocaine The ten sections Styrene-isoprene-styrene block copolymer 1  
The 25 sections Alicycle group saturated-hydrocarbon resin 2 The 40 sections  
Polyisobutylene The ten sections Liquid paraffin The 15 sections Anti-oxidant The 0.1

sections 1 Clayton D-1117 (product made from shell \*\*\*\*\*)

2) \*\*\*\*\* P-90 (the Arakawa chemistry company make)

[0033] It is a lidocaine 2.14mg/cm like an example 1 2 The pasting agent to contain was obtained.

[0034] Example of a comparison It is a lidocaine 2.14mg/cm like an example 1 except not blending 1 oil component (liquid paraffin) 2 The pasting agent to contain was obtained.

[0035] Example of a comparison It is a lidocaine 2.14mg/cm like an example 1 except not blending 2 adhesion grant component (alicyclic group saturated-hydrocarbon resin) 2 The pasting agent to contain was obtained.

[0036] Example of a comparison 3 Poultice: Lidocaine The ten sections D sorbitol The ten sections Glycerol The 20 sections Propylene glycol The ten sections Sodium polyacrylate The four sections Carboxymethylcellulose sodium The five sections Polyacrylic acid The three sections Methyl parahydroxybenzoate The 0.1 sections Propylparaben The 0.05 sections Aluminum hydroxide The 0.3 sections Purified water Residue \*\* Amount The 100 sections

[0037] D sorbitol and the polyacrylic acid were added to the purified water, and it mixed. The liquid which carried out the mixed lysis of a propylene glycol and the lidocaine was added further there, and it mixed. The liquid which distributed sodium polyacrylate, carboxymethylcellulose sodium, an aluminum hydroxide, methyl parahydroxybenzoate, and the propylparaben in the glycerol was added to this mixture, and it fully mixed until it became uniform. Obtained \*\*\*\* is spread on a nonwoven fabric, a polyethylene-terephthalate film is stuck, and it judges in a suitable size, and is a lidocaine 10mg/cm 2 The pasting agent to contain was obtained.

[0038] Example of a comparison The pasting agent was obtained like the example 1 except replacing with a nonwoven fabric \*\*\*\* obtained in the four examples 1, and spreading it on a polyethylene film.

[0039] Example of a comparison The acrylic-acid-2-ethylhexyl 95 sections and the acrylic-acid 5 section were taught in the flask under 5 inert-gas ambient atmosphere, having added the azobisisobutyronitril 0.3 section and maintaining in temperature of 60 degrees C in ethyl acetate as a polymerization initiator, the polymerization was carried out and acrylic pressure-sensitive adhesives solution A (41.2% of solid contents) was obtained. To the solid-content 90 section of this solution, the lidocaine 10 section was added, ethyl acetate was added, and the solution of 35% of total solids was obtained. The obtained solution was applied to the releasing paper made from polyester, this was dried for 5 minutes at the temperature of 100 degrees C, and the lidocaine 10% inclusion pressure sensitive adhesive layer was obtained. The obtained lidocaine inclusion pressure sensitive adhesive layer was stuck on the base material made from polyester, and the pasting agent which contains 2.14mg /of lidocaines two times cm was obtained.

[0040] example of an examination one patch-test: -- the pasting agent (what was judged in the 10cmx7cm size) obtained in examples 1-3 and the examples 1-4 of a comparison was stuck on the side thorax (site from \*\* of shingles) which is the comparatively large fraction of a motion of the skin of a healthy adult of the skin The pasting status of after (after [ pasting ] 2 hours and, and 6 hours) was investigated.

[0041] (Result) A result is shown in Table 1 (n= 20). The pasting agent of examples 1-3 was often adhering to the skin until after 6 hours so that clearly from Table 1. However, since the pasting agent of the example 1 of a comparison did not have the flexibility of \*\*\*\*, its sticking tendency was weak. The pasting agent of the example 2 of a comparison did not have tackiness. The pasting agent of the example 3 of a comparison had weak adhesion compared with the thing of an example. Since the pasting agent of the example 4 of a comparison did not have the elasticity of a base material and did not follow a motion of the skin, it was turned over and defluxion generated it.

[0042]

[Table 1]



	各貼付状態に対応する人数 (20人中)					
	貼付2時間後			貼付6時間後		
	めくれ なし	少し めくれ	脱落	めくれ なし	少し めくれ	脱落
実施例1	20	0	0	20	0	0
実施例2	20	0	0	20	0	0
実施例3	20	0	0	20	0	0
比較例1	0	5	15	0	0	20
比較例2	0	0	20	0	0	20
比較例3	0	17	3	0	15	5
比較例4	0	18	2	0	10	10

[0043] Example of an examination Determination of the amount of the lidocaine which penetrates the pars-abdominalis extraction skin of a hair loess mouse was carried out by HPLC using the 2 medicine permeability examination: Francis type diffusion cell. The pasting agent obtained in the examples 1 and 2 and the examples 3 and 5 of a comparison was pierced in a circle with a diameter of 1.7cm, respectively, and it stuck on the skin of a diffusion cell. To the receptor side, receptor liquid was extracted with time using pH 6.8 phosphate buffer solution, and the amount of medicine transparency was measured.

[0044] (Result) A result is shown in drawing 1 (n= 3). The medicine penetrated the skin of a hair loess mouse with time, and the permeability was excellent in the pasting agent of examples 1 and 2 compared with the example of a comparison so that clearly from drawing. Pasting agent of the example 3 of a comparison On the whole, permeability was low. Moreover, although the pasting agent of the example 5 of a comparison did not have an example and a difference till 6 hours after examination start, the amount of transparency did not increase after it.

[0045] example of an examination three pharmacological tests: -- six points of having stimulated a tablet pasting schedule field by the mandrin, and sensing an ache were beforehand chosen to the forearm circles side of an adult of the healthy skin, and the mark was put Next, the pasting agent obtained in the examples 1 and 2 and the examples 3 and 5 of a comparison was stuck on the field. The fraction which put the mark with time after pasting was stimulated by the mandrin, and the number of the points of having sensed the ache among six points was used as the score of an ache.

[0046] (Result) A result is shown in drawing 2 (n= 3). About the pasting agent of examples 1 and 2, the effect was quickly discovered after pasting and it continued for a long time so that clearly from drawing. The pasting agent of the example 3 of a comparison had the weak effect. Moreover, the durability of an effect was not enough although the pasting agent of the example 5 of a comparison demonstrated the effect quickly like the example immediately after pasting.

[0047] Example of an examination The pasting agent obtained in the example 1 per a 4 clinical-trial: shingles patient and three after [ shingles ] neuralgai patients each and the examples 3 and 5 of a comparison was applied after the time of rising, and bathing (or before sleeping) twice per day, and the mitigation effect of the ache was investigated. The ache measured the extent by the visual analog graduation method (VAS; Visual Analogue Scale Method).

[0048] (Result) A result is shown in drawing 3. The pasting agent of an example 1 is effective in mitigation of the ache accompanied by these morbus, and it was checked that an effect is superior to the thing of the example of a comparison so that clearly from drawing. Since it was inferior to tackiness and adhesion was not [ that the absorptivity of a medicine is inadequate, and ] perfect, the pasting agent of the example 3 of a comparison was considered to be what has the weak effect as a result. Moreover, the pasting agent of the example 5 of a comparison was considered to be what has the weak effect from the property that it is inferior to

durability.

[0049]

[Effect of the Invention] The pasting agent of this invention can make \*\* medicine emit efficiently quantitatively, and it has the property which was [ lead / pasting covering \*\* long time is possible, and / to an improvement of a patient's compliance ] excellent while \*\* operation is simple. And since it excels in the durability of a pain relaxation effect and it excels in the tackiness to an application site, and flattery nature, the after [ shingles or shingles ] neuralgai etc. is a tablet very suitable for the purpose of pain relief.

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**DESCRIPTION OF DRAWINGS**

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**[Brief Description of the Drawings]**

**[Drawing 1]** It is the drawing in which the test result of the pasting agent of the examples 1 and 2 and the examples 3 and 5 of a comparison is shown, and transition of the amount of medicine transparency to pasting time and it is shown.

**[Drawing 2]** It is the drawing in which the test result of the pasting agent of the examples 1 and 2 and the examples 3 and 5 of a comparison is shown, and a number (score) of a point of change which sensed the ache to pasting time and the time after elimination is shown.

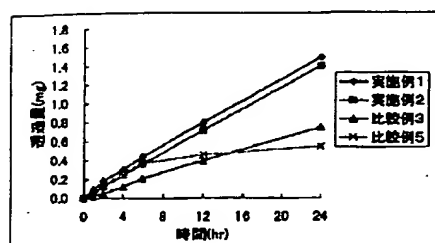
**[Drawing 3]** It is the drawing in which the test result of the pasting agent of the example 1 and the examples 3 and 5 of a comparison is shown, and change of VAS of the ache to pasting time is shown.  
with -- Top

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**[Translation done.]**

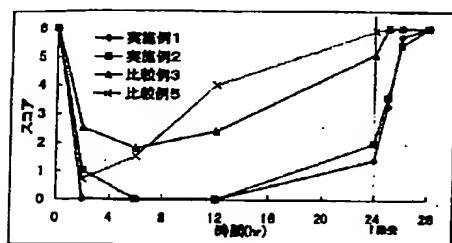
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Drawing selection Drawing 1

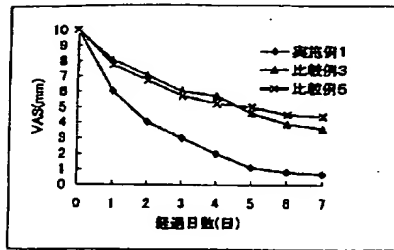


[Translation done.]

Drawing selection Drawing 2



[Translation done.]

Drawing selection Drawing 3

[Translation done.]